

[0011] Chemotherapeutic agents mainly affect cells that are undergoing division or DNA synthesis, thus slow growing malignant cells, such as lung cancer or colorectal cancer, are often unresponsive. Furthermore, most chemotherapeutic agents have a narrow therapeutic index. Common adverse effects of chemotherapy include vomiting, stomatitis, and alopecia. Toxicity of the chemotherapeutic agents is often the result of their effect on rapidly proliferating cells, which are vulnerable to the toxic effects of the agents, such as bone marrow or from cells harbored from detection (immunosuppression), gastrointestinal tract (mucosal ulceration), skin and hair (dermatitis and alopecia).

[0012] Many potent cytotoxic agents act at specific phases of the cell cycle (cell cycle dependent) and have activity only against cells in the process of division, thus acting specifically on processes such as DNA synthesis, transcription, or mitotic spindle function. Other agents are cell cycle independent. Susceptibility to cytotoxic treatment, therefore, may vary at different stages of the cell life cycle, with only those cells in a specific phase of the cell cycle being killed. Because of this cell cycle specificity, treatment with cytotoxic agents needs to be prolonged or repeated in order to allow cells to enter the sensitive phase. Non-cell-cycle-specific agents may act at any stage of the cell cycle; however, the cytotoxic effects are still dependent on cell proliferation. Cytotoxic agents thus kill a fixed fraction of tumor cells, the fraction being proportionate to the dose of the drug treatment.

[0013] Numerous neoplasia-treating agents are currently in use today, including any chemotherapeutic agents, and biotherapeutic agents as well as radiation therapy. There are numerous types of chemotherapeutic agents, including alkylating agents, nitrosoureas, antimetabolites, antitumor antibiotics, mitotic inhibitors, corticosteroid hormones, sex hormones, immunotherapy or others such as L-asparaginase and tretinoin. Some are briefly discussed below.

[0014] A widely used current chemotherapeutic agent is gemcitabine. Gemcitabine is a pyrimidine analogue that belongs to a general group of chemotherapy drugs known as antimetabolites and that also acts as a radiation-sensitizing agent. Gemcitabine exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis, i.e., the S-phase, and also blocks the progression of cells through the G₁/S-phase boundary.

[0015] Gemcitabine is an approved chemotherapeutic agent for a wide range of tumors that include, but are not limited to, pancreatic and colorectal carcinoma. The efficacy of gemcitabine is marginal, however, and life expectancy is rarely extended, particularly for pancreatic cancer patients. Side effects of gemcitabine administration are relatively mild when compared to other chemotherapeutic agents, consisting of myelosuppression with increased risk of infection, decreased platelet count with increased risk of bleeding, nausea, vomiting, increased liver function blood tests and fatigue. Gemcitabine, in general, however, has replaced other therapies because of its less toxic effects on the patient, and hence, a better quality of life.

[0016] The platinum family of chemotherapeutics consists primarily of cisplatin and carboplatin. Cisplatin is an inorganic platinum complex that disrupts the DNA helix by forming intra- and interstrand cross-links. Cisplatin also reacts, however, with nucleophils of other tissues, causing toxic effects on the kidney and on the eighth cranial nerve (which is responsible for causing intense nausea and vom-

iting). Other side effects include renal toxicity, ototoxicity manifested by tinnitus and hearing loss, and mild to moderate myelosuppression. Carboplatin differs from cisplatin mainly with respect to side effects. Myelosuppression is the dose-limiting toxicity for carboplatin with very little of the renal, neurologic, or ototoxicities that are encountered with cisplatin.

[0017] Paclitaxel is a natural, although quite toxic, substance derived from the yew tree that is chemically altered to produce a powerful anti microtubule chemotherapeutic agent indicated for the treatment of metastatic breast cancer, metastatic ovarian cancer, and Kaposi's sarcoma. Paclitaxel also has been used to treat SCCHN, non-small cell lung cancer, small cell lung cancer and bladder cancer. Side effects commonly encountered with paclitaxel administration include nausea and vomiting, loss of appetite, change in taste, thinned or brittle hair, pain in the joints of the arms or legs lasting 2-3 days, changes in the color of nails and tingling in hands or toes.

[0018] The chemotherapeutic agent, 5 fluorouracil (5-FU), has been one of the major antimetabolites used in a variety of solid cancers since the 1960s. 5-FU prevents cells from making DNA and RNA by interfering with the synthesis of nucleic acids, thus disrupting the growth of cancer cells. 5-FU is used alone or in combination in the adjuvant treatment of breast, colon, gastrointestinal and head or neck cancer. 5-FU also is used as a palliative therapy of inoperable malignant neoplasms, such as of the gastrointestinal tract, breast, liver, genitourinary system and pancreas. 5-FU has many common side effects, including myelosuppression with increased risk of infection and bleeding, darkening of skin and nail beds, nausea, vomiting, sores in mouth or on the lips, thinning hair, diarrhea, brittle nails, increased sensitivity to the sun and dry, flaky skin.

[0019] There exists a need, therefore, for a therapeutic formulation to treat various types of cancer and, in particular, pancreatic cancer and SCCHN, which demonstrates enhanced efficacy and survival rates with reduced concomitant side effects and toxicity commonly encountered with chemotherapeutic agents.

SUMMARY OF THE INVENTION

[0020] The present invention provides for the first time a carcinotherapeutic pharmaceutical composition and/or treatment method for treating neoplasias in an animal or human comprised of a carrier and therapeutically effective amounts of at least one neoplasia treating agent, such as chemotherapeutic agent or radiation therapy (agent) and the biotherapeutic endogenous pentapeptide Met-enkephalin, referred to as opioid growth factor (OGF). As used herein, a carcinotherapeutic composition refers to a composition that includes both chemotherapeutic and biotherapeutic agents for the treatment of all neoplasias, including but not limited to true carcinomas but also other cancers such as sarcomas, melanomas, etc.

[0021] As used herein the term "OGF or Met-enkephalin" shall be interpreted to include all modifications, substitutions, truncations or derivatives of OGF or Met-enkephalin which retain the ability to interact with the OGF receptor in a similar fashion to OGF as described herein. This also includes synthetic or any other compound which mimics the biological activity of OGF in its interaction with the OGF receptor.